42. A method of claim 41 wherein the aggregates have a particle size of from about 20 nm to 1 μm.

43. A method of claim 28 wherein a pharmaceutical composition comprising the active enamel substance is administered to the mammal.

44. A method of claim 43 wherein the pharmaceutical composition comprises a pharmaceutically acceptable excipient.

45. A method of claim 44 wherein the pharmaceutically acceptable excipient is propylene glycol alginate.

46. A method of claim 44 wherein the pharmaceutically acceptable excipient is hyaluronic acid or a salt or derivative thereof.

REMARKS

Applicants appreciate the indication that claims 28-31 are free of the prior art.

The specification and claims 28 and 29 have been amended, and claims 32-46 were added. No new matter has been added by virtue of the amendments. For instance, support for the amendments appears e.g. in the original claims of the application.

Claims 28-31 were rejected under 35 U.S.C. 112, first paragraph. In the Office Action, it is specifically acknowledged that the present application is "enabling for a method for treating malignant cancer cell lines such as those listed in Table 1 ..." However, the position is taken that the present claims do not satisfy the requirements of Section 112, first paragraph. No substantiating reasons have been provided for that position; rather, the data of record is critiqued in support of the rejection. The rejection is traversed.

The present application fully satisfies the requirements of Section 112, including the "how to make" and "how to use" requirements of Section 112, first paragraph.

For instance, at pages 7-8 of the application, preferred enamel matrix proteins for use in the claimed methods are disclosed. Preparation of compositions for administration in accordance with the invention are disclosed at pages 9-10 of the application. Preparation and use of administration compositions are disclosed at pages 11 through 13 of the application. Preferred compositions and administration procedures are disclosed at pages 14 through 19 of the application. Preferred dosage amounts and administration protocols are disclosed at pages 19 through 20 of the application.

The application still further includes **NUMEROUS WORKING EXAMPLES** which demonstrate the invention.

In view of such extensive disclosure, the skilled worker clearly would have been able to make and use the claimed subject matters.

To specifically respond to at least some of the points raised in the Office Action, the "cell lines" as described in the Office Action are primary tissue cultures from human tumor tissues, as disclosed at Example 3 on page 24, lines 25-27 and page 5, lines 9-14 of the application. In contrast to cell lines, primary tissue cultures are non-transformed cells and thus represent a system closely resembling *in vivo* conditions.

The controls of Examples 2 and 3 are clearly disclosed in the application and the results for those controls shown. See page 25, lines 17-19, page 25, lines 6-7 and Figures 1-3 of the application. In Example 2, HeLa cells cultured under similar conditions in the absence of EMD are used as controls and the results are shown in parallel, whereas the results of the cultures in Example 3 are presented as the ratio between EMD treated cells and untreated cells.

Moreover, since the filing of the application, others have shown that EMD has cytostatic effect on neoplastic cells. See Kawase et al., Journal of Periodontal Research, 35:291-300 (2000), copy enclosed.

Moreover, absolutely no sustainable substantiating reasons or supporting evidence have been presented in the Action to establish **why** one skilled in the art could not make and use the claimed subject matter based on Applicants' disclosure. Rather, the instant rejection appears premised on unsupported criticisms of Applicants' disclosure. The citation of a document published in the year 1975 (see page 5 of the Office Action) is not seen as particularly relevant here.

Such a basis for rejection under Section 112, first paragraph is simply not proper. It is well established that in the absence of any evidence why a supporting disclosure is not sufficient, the mere allegation if inadequacy is not considered to constitute a satisfactory basis for rejection under Section 112, first paragraph. Thus, for example, Section 2164.04 of the Manual of Patent examining Procedure mandates the following:

> In order to make [an enablement] rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.
>
> ***
>
> As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of it own with acceptable evidence of reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go the trouble and expense of supporting his presumptively accurate disclosure.

Additionally, Section 112 clearly does not require absolute predictability with respect to the practice of every possible embodiment of a claimed invention, a requirement that the instant rejection appears to impose on Applicants. For example, in the chemical case of *In re Angstadt*, the CCPA reversed a rejection under Section 112, first paragraph and stated (190 USPQ at 219: bold emphasis added):

> Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure ... Without undue experimentation or effort or expense the combinations which do not work will be readily discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable n advance, which is impracticable and unreasonable.

In view thereof, reconsideration and withdrawal of the rejection under Section 112, first paragraph are requested.

Claims 28-31 were rejected under 35 U.S.C. 112, second paragraph. The rejection is traversed.

The skilled worker can readily understand the claim language, particularly when those claims are read in light of the supporting specification, as is proper.

For instance, the term "treating" is recited in claims of an extremely large number of issued patents, thus showing that the term is not indefinite. The tem is fully recognized as acceptable under Section 112, second paragraph.

Additionally, the term "affected" in claim 29 also would be readily understood, particularly in view of the application as a whole.

Similarly, the term "enamel substance" is well understood, especially in view of the extensive disclosure of the application. The skilled worker also would understand what constitutes derivatives. See the application at page 5, line 35-page 10, line 8. Indeed, particularly suitable materials can be identified by simple testing.

In view thereof reconsideration and withdrawal of the rejection are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

Peter F. Corless, Reg. No. 33,860
EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman IP Group
130 Water Street
Boston, Massachusetts 02109-4280
Tel. (617) 523-3400
Fax (617) 523-6440

VERSION WITH AMENDMENTS MARKED

28. (amended) A method for [preventing or] treating malignant or benign neoplasms, the method comprising to a mammal in need thereof a [prophylactically] therapeutically effective amount of an active enamel substance.

29. (amended) A method according to claim 28, wherein the active enamel substance is applied in an amount of total protein per cm^2 area of affected tissue corresponding from about 0.01 mg/cm^2 to about 20 mg/cm^2[, such as from about 0.1 mg/cm2 to about 15 mg/cm^2].